Kidney360

Comparative Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Serum Electrolyte Levels in Patients with Type 2 Diabetes: A Pairwise and Network Meta-Analysis of Randomized Controlled Trials

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Key Points

- The relative efficacy of each specific sodium-glucose co-transporter 2 inhibitor compared with the other in affecting electrolytes has rarely assessed in head-to-head trials.
- The study aimed to maximize statistical power to summarize direct and indirect evidence using both pairwise and network meta-analyses.
- Sodium-glucose co-transporter 2 inhibitors significantly increased serum magnesium and phosphate levels, supporting a class effect of sodium-glucose co-transporter 2 inhibition.

Abstract

Background Previous studies have reported that sodium-glucose co-transporter 2 (SGLT2) inhibitors (SGLT2is) affect levels of serum electrolytes, especially magnesium. This study aimed to integrate direct and indirect trial evidence to maximize statistical power to clarify their overall and comparative effects in patients with type 2 diabetes (T2D).

Methods We systematically searched PubMed, EMBASE, CENTRAL, and ClinicalTrials.gov up to January 2021 to identify eligible randomized controlled trials (RCTs) of SGLT2is that reported mean changes in serum electrolytes, including magnesium, sodium, potassium, phosphate, and calcium. We performed both random-effects pairwise and network meta-analyses to calculate the weighted mean difference (WMD) and 95% confidence intervals (CI).

Results In total, we included 25 RCTs involving 28,269 patients with T2D and 6 SGLT2is. Compared with placebo, SGLT2is were significantly associated with elevations in serum magnesium by 0.07 mmol/L (95% CI, 0.06 to 0.08 mmol/L) and serum phosphate by 0.03 mmol/L (95% CI, 0.02 to 0.04 mmol/L). Our network meta-analysis showed no evidence of significantly superior efficacy of any specific SGLT2 inhibitor over the others, although dapagliflozin was associated with a larger increment in serum magnesium (WMD=0.16 mmol/L) compared with other SGLT2is. Similarly, no statistically detectable differences among the effects of SGLT2is on serum levels of other electrolytes were detected.

Conclusions SGLT2is significantly increased serum magnesium and phosphate levels, consistent with a class effect of SGLT2 inhibition. However, further investigations of long-term efficacy and safety in patients with T2D with different clinical phenotypes are needed.

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Introduction

Sodium-glucose cotransporter (SGLT) 2 inhibitors (SGLT2is) are a novel class of glucose-lowering agents that are indicated for the treatment of type 2 diabetes (T2D). SGLT2is selectively inhibit renal glucose reabsorption and increase urinary glucose excretion (1). Besides hypoglycemic effects in patients with T2D, SGLT2is have been considered an effective treatment option for renal and cardiovascular protection in diabetic patients with CKD (2–4). More recently, dapagliflozin was shown to extend its renal-protective effect to patients without diabetes (5).

SGLT2 is mainly expressed in renal tissue (6) but not in the human heart (7), where only SGLT1 is

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expressed at low levels. Therefore, the potential benefit of SGLT2is is likely through the kidney. SGLT2is blocks reabsorption of sodium and other electrolytes coupled with sodium, and although the effects of SGLT2is on electrolyte balance may play a critical role in improving cardiovascular and kidney outcomes, those contentions will need to be confirmed by more evidence.

The mechanisms underlying renal and cardiovascular protection by SGLT2is remain unresolved. The data on renal electrolyte handling in individuals with T2D using SGLT2is are limited. Several previous studies have examined the head-to-head effects of different SGLT2is in conventional pairwise meta-analyses. Yet, many of these direct comparison results lacked statistical power to test a SGLT2is class effect or a specific drug effect on electrolytes (8). Given the fact that few of comparisons between any two of SGLT2i have been studied in head-to-head trials, the relative efficacy of a given SGLT2 inhibitor compared with others in influencing electrolytes has never been systematically or quantitatively assessed. The current study was designed to maximize statistical power to examine whether and to what extent SGLT2is affect serum electrolyte levels in patients with T2D. With accumulating trial data, we conducted both pairwise and network meta-analyses to summarize both direct and indirect evidence on the basis of available data from randomized controlled trials (RCTs).

Materials and Methods

Search Strategy and Selection of Articles

We searched PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Clinical Trials.gov up to January 2021 to identify eligible RCTs using relevant search terms without restriction of language or year of publication. We included parallel RCTs of at least 24 weeks' duration that compared SGLT2is with placebo in adult patients with T2D and reported mean postintervention changes in electrolyte levels from baseline in each group or the data that allowed us to estimate the mean changes and their variances. Our outcomes included serum levels of magnesium, phosphate, calcium, sodium, and potassium. Six commonly prescribed SGLT2is were chosen for study: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, and bexagliflozin.

Data Extraction and Quality Assessment

We collected the following information from each eligible RCT: first author, publication year, study characteristics (country of origin, design, and funding), patients' characteristics (inclusion criteria, background treatments, mean age, race, baseline glycated hemoglobin [HbA1c], mean eGFR, and body mean index), interventions (type and dose of SGLT2is), and the mean values (electrolyte level), variance measure, and the number of participants in the treatment and control arms for all reported periods.

The Cochrane risk-of-bias tool was used to assess the quality of RCTs on the basis of five domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias). Three reviewers independently extracted the data; they were all blinded to the authors and institutions of the studies undergoing review. Any disagreements were resolved by consensus or referral to a third reviewer.

Statistical Analyses

For pairwise meta-analyses, we applied the classic DerSimonian and Laird's method using inverse variance weights to combine the weighted mean difference (WMD) estimates as reported or derived from the original reports. Heterogeneity between studies was assessed by the Cochrane Q (P value) and I^2 statistics. The Q statistic is a chi-squared test for heterogeneity, and the I^2 is the percentage of observed variance in effect sizes across studies. A value of 0% indicates no observed heterogeneity. Heterogeneity can be quantified as low, moderate, high, or considerably high, with ranges of 0%–25%, 25%–50%, 50%–75%, and 75%–100% for I^2, respectively.

In the absence of direct comparisons between two treatments, a network meta-analysis can be used to integrate a network of available evidence to allow for both direct and indirect comparisons between treatments for a specific outcome (9,10). For comparative effects of different SGLT2is on each electrolyte, a network meta-analysis in a frequentist framework using multivariate meta-analysis and meta-regression was constructed so that the effects of different SGLT2is on the same electrolyte were compared indirectly. The network meta-analysis was performed with STATA v16.1 (StataCorp, College Station, TX) using the "mvmeta" command and programmed STATA routines (9,10). To rank the SGLT2is for a specified outcome, we estimated the relative ranking probabilities of each treatment using surface under the cumulative ranking curve (SUCRA) probabilities and mean ranks. Higher SUCRA probability and lower mean rank indicate a larger intervention (11). The heterogeneity variance (τ) estimated by a restricted maximum likelihood method was used to quantify between-study heterogeneity for each outcome (12). In addition, a comparison-adjusted funnel plot was used to assess small-study effects within a network of interventions, with symmetry around the summary effect line indicating the absence of small-study effects (13). The result revealed no small-study effects, which indicated the absence of any over- or underestimate of the effect of SGLT2is.

All analyses were conducted using STATA/SE v16.1 for Windows (StataCorp). P values are based on two-sided hypothesis tests. A P value of <0.05 was considered statistically significant.

Results

Of the 5429 articles identified from electronic databases up to January 2021, after titles and abstracts were screened and duplicate studies were removed, 330 full-text articles were reviewed for further assessment. Twenty-five trials comparing SGLT2is with placebo met inclusion criteria and were included in the meta-analysis (Figure 1), encompassing a total of 28,269 participants with T2D (Table 1).

Baseline characteristics of the included trials are shown in Table 1. All trials enrolled participants with T2DM and compared SGLT2is with their respective placebo groups.

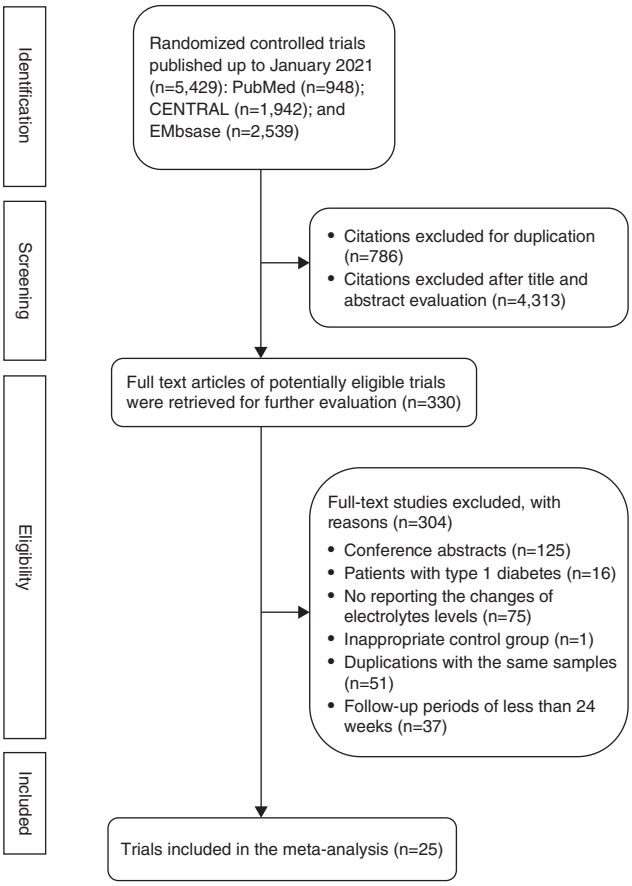

Figure 1. | Flow chart of the identification of eligible trials.

Overall, six different SGLT2is were studied; there were five trials of 11,936 (42%) participants for canagliflozin, four trials of 1530 (5%) participants for dapagliflozin, 10 trials of 12,518 (44%) participants for empagliflozin, three trials of 1588 (6%) participants for ertugliflozin, two trials of 313 (1%) participants for ipragliflozin, and one trial of 384 participants for bexagliflozin. The mean age of participants was 58 years, and the median trial duration was 58.7 weeks.

Risk-of-Bias Assessment

The overall risk of bias is presented in Supplemental Figure 1. The generation of random numbers was well performed in most trials. One open-label trial was assessed as having a high risk of performance bias for blinding of participants and personnel. Because electrolyte levels were measured in the lab (which is seldom influenced by outcome evaluators), the domain of blinding of outcome assessment was assessed as low risk. The risk of selective reporting (reporting bias) for all trials was considered low due to electrolyte outcomes reported in these trials.

Direct Head-to-Head Evidence from Pairwise Meta-Analysis

Despite significant between-trial heterogeneity (I^2=94%), most trials (except two) showed significantly elevated magnesium levels among patients using SGLT2is (Figure 2A). Overall, SGLT2is were significantly associated with increases in magnesium of 0.07 mmol/L (95% confidence interval [CI], 0.06 to 0.08 mmol/L).

For serum phosphate levels, nearly half the trials (n=11) showed a significant increase in phosphate among participants using SGLT2is, while the others (n=15) showed no effect or nonsignificant increments (Figure 2B). Overall, there is a statistical trend toward phosphate levels being elevated by SGLT2is (WMD=0.03 mmol/L; 95% CI, 0.02 to 0.04 mmol/L), although heterogeneity was significant (I^2=87%).

Of 19 trials with calcium data, only three showed a significant association with increased calcium, all of which used empagliflozin (Supplemental Figure 2A). Obviously, the final meta-analysis result was heavily weighted by the two trials that contributed to 67% of the weight. Overall, the SGLT2is were significantly associated with elevated levels of calcium by 0.01 mmol/L (95% CI, 0 to 0.01 mmol/L), but the result was not significant after removing these two trials.

In contrast, the pairwise meta-analysis results did not show significant effects of SGLT2is on serum levels of potassium (WMD=0; 95% CI, –0.02 to 0.02) or sodium (WMD=0.16; 95% CI, –0.02 to 0.35; Supplemental Figure 2, B and C). Compared with serum magnesium, phosphate, and calcium, the trials of serum sodium and potassium showed more heterogenous results in terms of the association direction and magnitude and statistical significance.

Comparative Evidence from Network Meta-Analysis

Figure 3A shows the network diagrams of direct comparison of specific classes of SGLT2is for magnesium levels reflected by the solid lines, the number of studies by the size of the nodes, and the number of patients by the thickness of the lines. In total, there were 25 direct comparisons between five different SGLT2is and their respective placebo/control groups. Empagliflozin compared with placebo/control had the highest number of trials (n=12), with the largest contribution in the estimation to the entire network for response in magnesium levels.

We found a significant increase in serum magnesium among those taking canagliflozin (WMD=0.08; 95% CI, 0.02 to 0.13), dapagliflozin (WMD=0.16; 95% CI, 0.09 to 0.23), and empagliflozin (WMD=0.06; 95% CI, 0.03 to 0.1) compared with those taking placebo (Figure 3B). There were similar increasing trends among those taking either ertugliflozin or ipragliflozin, although statistical significance was not reached due to low power. Overall, there was no significant difference between these SGLT2is, although the use of dapagliflozin appeared to have a larger effect than canagliflozin.

Similarly, there is available information on 25 pairwise comparisons of five SGLT2is for serum phosphate levels (Figure 4A). The comparison with the highest number of included studies was empagliflozin (n=13). Some SGLT2is were significantly associated with elevations in serum phosphate (Figure 4B). Compared with placebo, dapagliflozin (WMD=0.04; 95% CI, 0.01 to 0.07) and empagliflozin (WMD=0.02; 95% CI, 0 to 0.03) were significantly associated with a trend toward increases in serum phosphate levels. There were similar small increases in phosphate among

Table 1. Characteristics of included studies

First Author (Year)	NCT	SGLT2i	Control	Sample Size (*n*)	Background Therapy	Mean Age (Years)	Race (Primary)	Mean HbA1c (%)	Mean BMI (kg/m^2)	Mean eGFR (ml/min per 1.73 m^2)	Follow-up (Weeks)
Yale (2014) (45)	NCT01064414	CANA	PLA	269	SU or INS	68.5	White	8	33	39.4	52
Wilding (2013) (46)	NCT01106625	CANA	PLA	469	MET+SU	56.8	White	8.1	33.1	NR	52
Bode (2015) (47)	NCT01106651	CANA	PLA	714	OAD	63.6	White	7.7	31.6	77.5	104
Forst (2014) (48)	NCT01106690	CANA	PLA	342	MET+PIOG	57.4	White	7.9	32.5	86.4	26
Zhou (2019) (49)	NCT01032629, NCT01989754	CANA	PLA	10142	Standard care	63.3	White	8.3	32	76.5	130
Ferrannini (2010) (50)	NCT00528372	DAPA	PLA	274	Naïve treatment	52.2	White	7.9	32.6	NR	24
Wilding (2012) (51)	NCT00673231	DAPA	PLA	800	INS±OAD	59.3	White	8.5	33.1	NR	48
Bolinder (2014) (52)	NCT00855166	DAPA	PLA	182	MET	60.7	White	7.2	31.9	84.3	102
Bailey (2015) (53)	NCT00528372	DAPA	PLA	274	MET	56.5	White	8	NR	85.9	102
Roden (2013) (54)	NCT01177813	EMPA	PLA AND SIT	899	Naïve treatment	55	Asian	7.9	28.4	87.4	76
Barnett (2014) (55)	NCT01164501	EMPA	PLA	741	OAD	63.9	White	8	30.7	53.2	52
Häring (2014) (56)	NCT01159600	EMPA	PLA	638	MET	55.7	White	7.9	29.2	89	24
Haering (2015) (57)	NCT01159600	EMPA	PLA	666	MET+SU	57.1	Asian	8.1	28.2	87.2	76
Kovacs (2014) (58)	NCT01210001	EMPA	PLA	498	PIOG±MET	54.5	Asian	8.1	29.2	85.7	24
Rosenstock (2014) (59)	NCT01306214	EMPA	PLA	563	INS	56.7	White	8.3	34.8	84	52
Lewin (2015) (60)	NCT01422876	EMPA±LINA	LINA	667	MET	54.6	White	8	31.6	88.9	52
Rosenstock (2015) (61)	NCT01011868	EMPA	PLA	494	INS±OAD	58.8	White	8.2	32.2	84	78
Søfteland (2017) (62)	NCT01734785	EMPA	PLA	332	MET+LINA	55.2	White	7.97	30.2	92.3	24
Aronson (2018) (63)	NCT01958671	ERTU	PLA	461	Naïve treatment	56.4	NR	8.2	33	87.7	52
Rosenstock (2018) (64)	NCT02033889	ERTU	PLA	621	MET	56.6	White	8.1	30.9	90.5	26
Ji (2019) (65)	NCT02630706	ERTU	PLA	506	MET	56.5	Asian	8.1	26	99.3	26
Lu (2016) (66)	NCT01505426	IPRA	PLA	170	MET	53	Asian	7.7	26.8	149.3	24
Han (2018) (67)	NCT02452632	IPRA	PLA	143	MET_SITA	57.5	Asian	7.9	25.8	90	24
Halvorsen (2019) (68)	NCT03115112	BEXA	sitagliptin	384	MET	59.4	White	8	31.7	NR	24
Zinman (2015) (69)	NCT01131676	EMPA	PLA	7020	Standard care	63.2	White	8.1	30.6	74	160

NR, not reported; BMI, body mass index; EMPA, empagliflozin; ERTU, ertugliflozin; DAPA, dapagliflozin; CANA, canagliflozin; BEXA, bexagliflozin; PLA, placebo; MET, metformin; SIT, sitagliptin; SAXA, saxagliptin; LINA, linagliptin; SU, sulfonylureas; OAD, oral antidiabetic drugs; INS, insulin. PIOG, pioglitazone; IPRA, ipragliflozin.

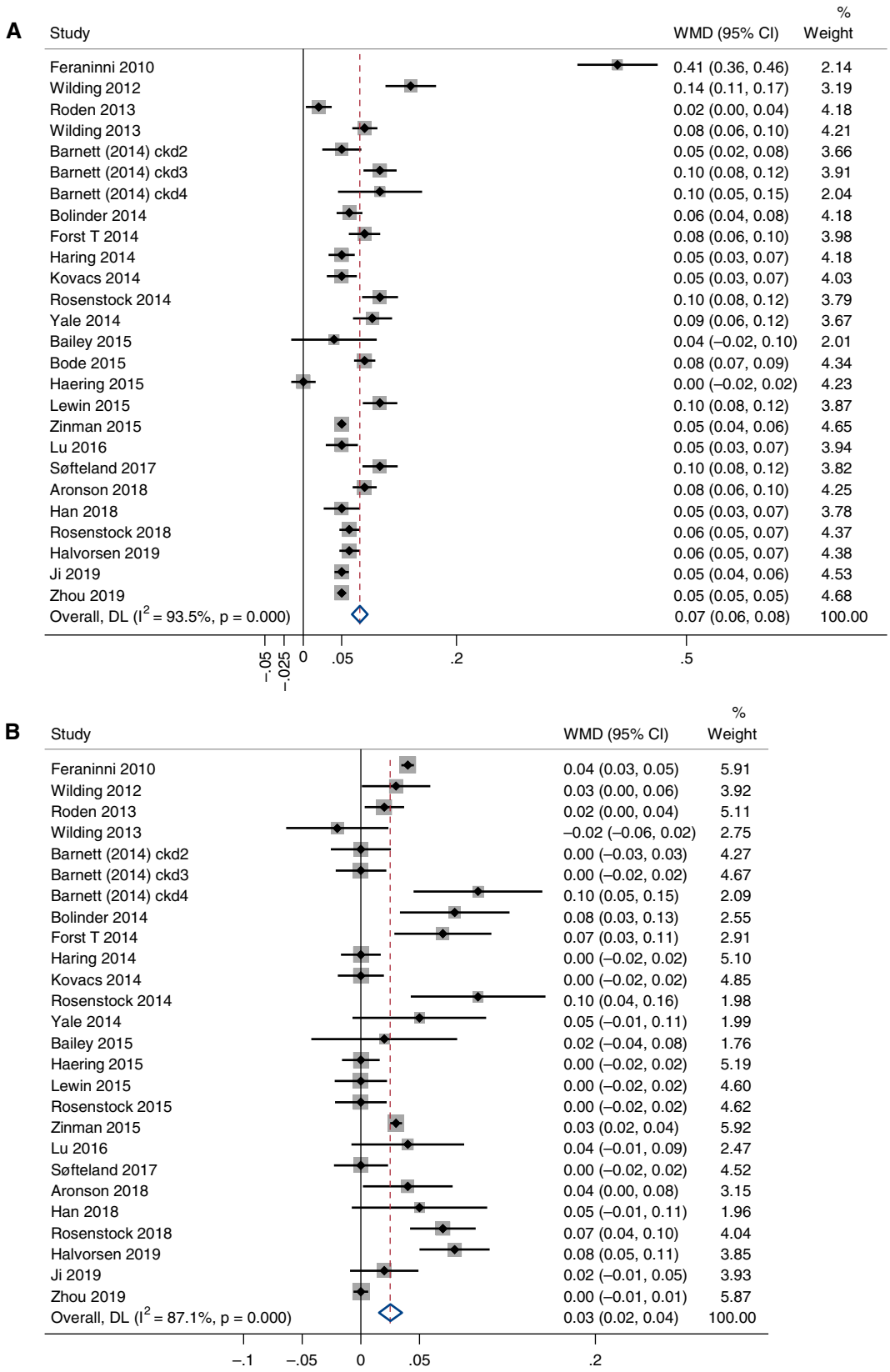

Figure 2. | **Pairwise meta-analyses of the effects of sodium-glucose cotransporter (SGLT) 2 inhibitors (SGLT2is) on magnesium and phosphate.** (A) Blood magnesium levels (mmol/L) and (B) blood phosphate levels (mmol/L). Each square indicates the WMD in each trial. The horizontal line represents the 95% CI. The pooled WMD and 95% CI is indicated by the dashed line and diamond. The black vertical line represents the null hypothesis. Heterogeneity between studies was assessed by the I^2 statistics and Cochrane Q (*P* value). WMD, weighted mean difference; CI, confidence interval.

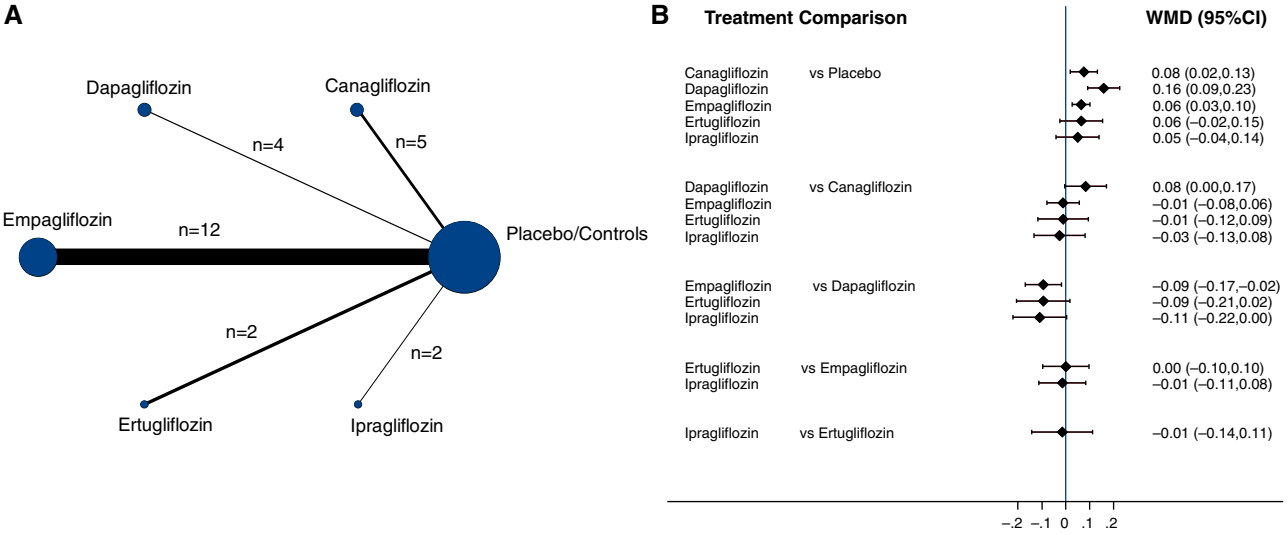

Figure 3. | **Network meta-analysis results of the effect of SGLT2is on blood magnesium levels.** (A) Network of eligible comparisons for the multiple-SGLT2is meta-analysis for effects on blood magnesium levels. Each node represents one treatment. The directly compared treatments are linked with a solid line; the width of the lines is proportional to the number of randomized participants (sample size), and the size of every node is proportional to the number of trials comparing every pair of treatments. (B) Network meta-analysis combining direct and indirect evidence within a network of eligible trials for the effects of SGLT2is on blood magnesium levels (mmol/L). The black solid lines represent the confidence intervals for WMD of blood magnesium levels for each comparison, and the blue line is the line of no effect (WMD=0).

those taking canagliflozin (WMD=0.02; 95% CI, –0.01 to 0.05), ertugliflozin (WMD=0.03; 95% CI, –0.01 to 0.07), and ipragliflozin (WMD=0.04; 95% CI, –0.01 to 0.09) but without statistical significance. There was no significant difference between any SGLT2is.

Levels of serum sodium were significantly higher among patients taking empagliflozin compared with those taking placebo (WMD=0.28; 95% CI, 0.06 to 0.49; Supplemental Figure 3). There was a modest increase in sodium among patients with ertugliflozin, and decreases with both canagliflozin and dapaliflozin, but without statistical significance. The overall effect of SGLT2is on serum sodium levels was not statistically significant. Again, there was no significant difference between any SGLT2is.

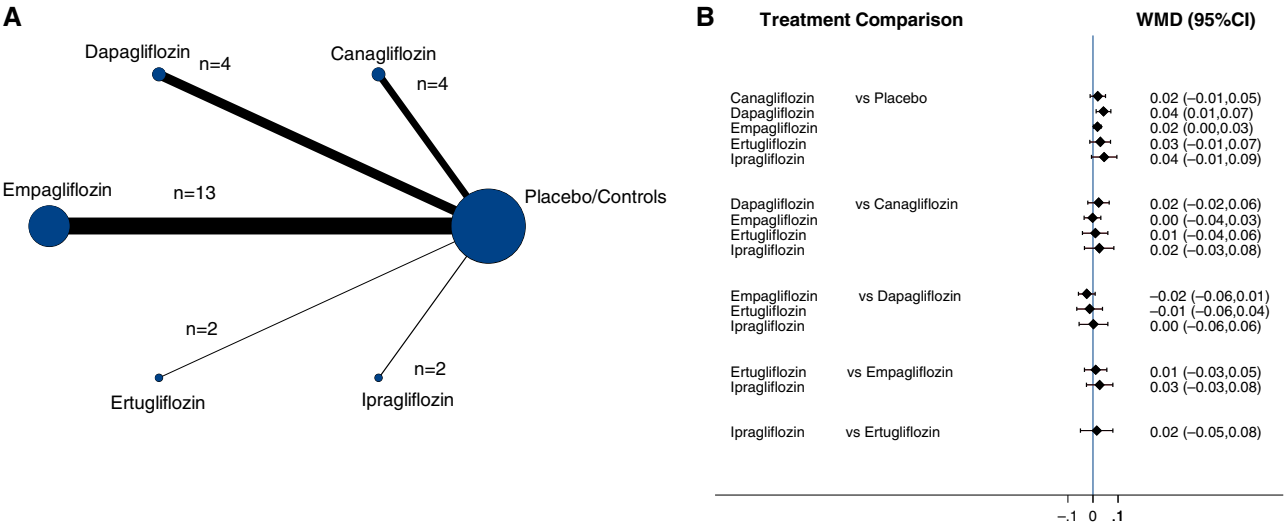

Figure 4. | **Network meta-analysis results of the effect of SGLT2is on blood phosphate levels.** (A) Network of eligible comparisons for the multiple-SGLT2is meta-analysis for effects on blood phosphate levels. Each node represents one treatment. The directly compared treatments are linked with a solid line; the width of the lines is proportional to the number of randomized participants (sample size), and the size of every node is proportional to the number of trials comparing every pair of treatments. (B) Network meta-analysis combining direct and indirect evidence within a network of eligible trials for the effects of SGLT2is on blood phosphate levels (mmol/L). The black solid lines represent the CIs for WMD of blood magnesium levels for each comparison, and the blue line is the line of no effect (WMD=0).

There were no significant differences in serum potassium levels; small increases in serum calcium levels were not clinically meaningful (Supplemental Figures 4 and 5).

Discussion

In this large meta-analysis of 25 RCTs involving 28,269 patients with T2D and six different SGLT2is, we found that SGLT2is significantly increased serum magnesium and phosphate levels, consistent with a class effect of SGLT2 inhibition. In contrast, there was no statistical evidence of differences in serum levels of other electrolytes produced by SGLT2is or specific SGLT2 inhibitor drugs.

Our results from both network and pairwise meta-analysis showed consistent evidence that SGLT2is significantly increase serum magnesium, further supporting our previous meta-analysis of available results from earlier trials (8). Collectively, previous trials documented the effect of SGLT2is on increasing serum magnesium. One *post hoc* analysis of 10 clinical trials showed that dapagliflozin corrected low magnesium in patients with T2D (14). Another report showed that three different SGLT2is relieved refractory hypomagnesemia in three patients, likely by blocking urinary magnesium wasting (15). SLGT2is also appeared to correct hypomagnesemia in patients with kidney transplant on tacrolimus (16). This treatment might also provide a benefit to kidney transplant recipients who experience chronic hypomagnesemia and improve renal- and cardiovascular-related outcomes. In addition, correcting hypomagnesemia may help glycemic control in diabetes but not *vice versa* (17).

The mechanism underlying the renal benefit of SGLT2is is likely to be independent of glucose levels and may possibly stem from a reduction in intraglomerular pressure (18) and other possible mechanisms presently being studied (19). SGLT2is can normalize proximal reabsorption *via* tubular glomerular feedback, which should have particular effects on glomerular hemodynamics, eliminate diabetic hyperfiltration, and improve hard renal end points (20,21).

Regulation of magnesium transport in the kidney occurs primarily in the thick ascending limb and distal convoluted tubules (22). In the thick ascending limb, both magnesium and calcium can activate the calcium-sensing receptor on the basolateral membrane and modulate paracellular magnesium transport (23). Other factors control magnesium transport through changes in the voltage and/or permeability of the paracellular pathway. SGLT inhibitors increased delivery of Na to the loop of Henle, which may increase magnesium absorption (24).

Serum magnesium levels are usually relatively stable, within a narrow range of 0.7–1 mmol/L in healthy adults. It is possible that even very small changes in serum magnesium levels are associated with an increased risk of renal and cardiovascular outcomes. In a meta-analysis of 48 randomized trials using oral magnesium supplements, an elevation in circulating magnesium of 0.05 mmol/L was observed in response to a wide range of doses of oral magnesium supplementation (25). Our study showed that SGLT2is produced 0.07 mmol/L increases in magnesium levels, which seems a minimal increment but is actually clinically meaningful. In 2016, an analysis of the prospective, population-based Rotterdam Study showed an inverse association between serum magnesium levels and mortality; a 0.1 mmol/L (0.24 mg/dl) increment of this ion was associated with 18% reduction in risk of coronary heart disease after 8.7 years follow-up (hazard ratio=0.82; 95% CI, 0.7 to 0.96) (26). The clinical significance of minimal change was also evident in a prospective study of 3525 British participants, which showed an inverse association between serum magnesium level and risk of incident heart failure. Lower magnesium levels were associated with impaired glycemic control, hypertension, and vascular calcification (27). *Vice versa*, higher magnesium levels can be beneficial for cardiovascular health, such as improvement of cellular respiration and cardiac output, and reduction in myocardial fibrosis (28).

We showed in a previous meta-analysis that blood phosphate was elevated in patients taking dapafliglozin (8). The current report, which includes more trial data and incorporates both direct and indirect evidence, shows similar results of SGLT2is on phosphate. The mechanism of phosphate elevation by SGLT2is is likely *via* the stimulation of renal proximal tubular reabsorption of phosphate through type 2 sodium-phosphate cotransporters (29,30). A small pharmacodynamic study showed that canagliflozin induced a prompt increase in serum phosphate, which triggered downstream changes in FGF23, 1,25-dihydroxyvitamin D, and parathyroid hormone in healthy volunteers (30). Decreases in 1,25-dihydroxyvitamin D levels with or without elevated parathyroid hormone were used to explain the possible risk of bone fracture associated with SGLT2is, but longer-term observation and additional data showed no evidence of increased risk of fracture (31,32). For individuals at high risk of fracture, phosphorus, calcium, and 25-dihydroxvitamin D levels should be monitored regularly, and a DEXA bone-density scan should also be performed regularly. Increased FGF23 levels may be an independent risk factor for cardiovascular outcomes (33), but most SGLT2is trials with potentially elevated FGF23 have shown improvements in cardiovascular outcomes. The discrepancy is likely due to the brevity of the pharmacodynamic study; FGF23 levels did not seem elevated after 24 weeks, even though phosphate was slightly higher. There is evidence of elevated cardiovascular mortality risk in patients with hyperphosphatemia (34–36). However, the balance between magnesium and phosphate may be more important for cardiovascular health and deserves further investigation (37).

SGLT2is rarely cause hypercalcemia. Our finding of increased calcium levels is mainly driven by two studies. A case report of a patient having hypercalcemia and diagnosed with primary hyperparathyroidism after dapagliflozin treatment is alarming (38). However, since primary hyperparathyroidism is a common condition, it remains unclear whether it could be caused by SGLT2is.

Our study showed no significant effect of SGLT2is on blood sodium or potassium levels, and the effects were similar across SGLT2is. These findings are consistent with previous reports on SGLT2is on blood sodium and potassium (39–42). Normally, kidneys reabsorb >99% of filtered sodium, with 4%–5% of filtered sodium acting as cotransporter of glucose through SGLT2. SGLT2 expression is increased in diabetes, contributing to a higher rate of glucose and sodium reabsorption. Inhibition of SGLT2

decreases reabsorption of sodium and glucose and leads to natriuresis and glycosuria. A randomized trial showed that empagliflozin led to a larger increase in blood sodium compared with placebo in treatment of hyponatremia due to the syndrome of inappropriate antidiuresis (43,44). However, the effect of empagliflozin on blood sodium levels was largely dependent on the severity of baseline hyponatremia, and the main difference between empagliflozin and placebo was severe hyponatremia, with blood sodium level <125 mmol/L. There were no clinically meaningful effects of SGLT2is on blood potassium level observed in prior trials of canagliflozin (42), dapagliflozin (40), or empagliflozin (44). Patients with diabetes were more likely to have hyperkalemia, especially when they also had reduced kidney function. Dapagliflozin was approved for patients with CKD without diabetes to slow down the progression of kidney disease on the basis of the lack of evidence of significant hyperkalemia in the SGLT2is arm of that trial (5).

Although our meta-analysis included a large number of available SGLT2is trials with electrolyte data, some limitations deserve consideration. First, many patients with T2D may also have hypertension. It is possible that they were more likely to be taking ACEI/ARB and diuretics, which could affect serum electrolytes. Due to randomized trial design, the percentage of such patients would likely be similar between treatment and control groups. Thus, inclusion of hypertensive patients would not invalidate the comparison but might have attenuated the precision of genuine effect estimates. Our analysis does not stratify the data on those medications. Second, although the effect of SGLT2is on magnesium may vary depending on different baseline magnesium status, most of the clinical trials included in the study do not have clear information on magnesium insufficiency/deficiency. Finally, because most of the trials did not recruit patients with impaired kidney function, the results are not to be generalized to patients with CKD.

In conclusion, our meta-analysis of randomized trial data showed that SGLT2is significantly increased serum magnesium and phosphate levels, representing a class effect of SGLT2 inhibition. These results call for long-term examination of efficacy and safety in patients with T2D with different clinical phenotypes in RCTs and real-world settings.

Disclosures

All authors have nothing to disclose.

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Author Contributions

Y. Huan, M. Leibensperger, B. Seo, and J. Zhang curated the data; Y. Huan, M. Leibensperger, B. Seo, Y. Song, and J. Zhang were responsible for validation; Y. Huan, M. Leibensperger, B. Seo, and J. Zhang wrote the original draft of the manuscript; B. Seo was responsible for funding acquisition; B. Seo and Y. Song were responsible for methodology; Y. Song and J. Zhang conceptualized the study; and Y. Song was responsible for the investigation, software, and supervision, and reviewed and edited the manuscript.

Supplemental Material

This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0006672021/-/DCSupplemental.

Supplemental Figure 1. Risk-of-bias assessments of individual trials.

Supplemental Figure 2. (A) Pairwise meta-analysis results of SGLT2 inhibitors on blood calcium levels. (B) Pairwise meta-analysis results of SGLT2 inhibitors on blood potassium levels. (C) Pairwise meta-analysis results of SGLT2 inhibitors on blood sodium levels.

Supplemental Figure 3. (A) Network of eligible comparisons for the multiple-SGLT2 inhibitors meta-analysis for effects on blood sodium levels. (B) Network meta-analysis of eligible trials for the effects of SGLT2 inhibitors on blood sodium levels (mmol/L).

Supplemental Figure 4. (A) Network of eligible comparisons for the multiple-SGLT2 inhibitors meta-analysis for effects on blood potassium levels. (B) Network meta-analysis of eligible trials for the effects of SGLT2 inhibitors on blood potassium levels (mmol/L).

Supplemental Figure 5. (A) Network of eligible comparisons for the multiple-SGLT2 inhibitors meta-analysis for effects on blood calcium levels. (B) Network meta-analysis of eligible trials for the effects of SGLT2 inhibitors on blood calcium levels (mmol/L).

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